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Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville MD 20852

RE: Docket No 2003N-0496
RIN 0910-AF09
Food Labeling: Health Claims; Dietary Guidance

To Whom It May Concern:

In the continuing discussion on "health claims", FDA proceeded down a seductive path of what seemed to be "bright lines" of distinction on claims to the point where there were only a few *procrustean* solutions; these solutions soon became so unsustainable that change was mandated by the *Whitaker* decision. Now comes an ANPR (Docket No. 2003N-0496) wherein the Agency asks for comment on set of options that would only create another set of rigid boundaries which would soon be outgrown. The three options presented are much like three fixed dinner menus, each with some desirable features, but also with features that are undesirable; such choice of one of the three options is more akin to a *Hobson's choice*, with the pragmatic choice as the one with the fewest undesirable characteristics.

To best serve the public, FDA must do four things: (1) FDA must maintain its sense of **flexibility** at the risk of having to periodically substitute one set of rigid rules and default assumptions for another. (2) FDA must make the **'disconnect' between substance and disease** for "health" claims and; recognize that not all substances will have the same effect on all or even a majority of the consumers. (3) FDA must **vest independent experts** (outside of government agencies), who can make scientifically sound, unbiased decisions, with the power to judge the validity of a claim. (4) FDA must permit a **term of exclusivity** for marketing a product, if the Agency ever expects to provide the incentive for responsible manufacturers to recoup their investment in safety and efficacy testing.

(1) FDA must maintain its sense of flexibility at the risk of having to periodically substitute one set of rigid rules and default assumptions for another. Micro-managing the process for attaining health claims (qualified or not) will not guarantee a perfect product. Clearly, it is too early in the evolution of "health claims" to assume that bright lines can be drawn. For example, dissecting claims and distinguishing them according to Level B, C and D, is based on the false hope that the body of evidence will allow for such a clear distinction. There will always

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be claims somewhere between B and C or C and D, that might not quite qualify as having attained a score on one "evidence-based scale" as opposed to another. At the root of all of these scales are qualitative judgments that cannot be made quantitative simply because of the number of reviewers or the layers of review. Exceptions to every rule will require endless rounds of reconsiderations and modifications and, regulation will eventually be by exception; it is simply too early to set specific criteria. If a bright line is needed for health claims, it should be whether the claim (statement) is truthful, not degrees of acceptance by the Agency for different levels of approval.

(2) FDA must make the 'disconnect' between substance and disease and; that not all substances will have the same effect on all or even a majority of consumers. FDA must make this disconnect because the concept is intrinsically hobbled by three factors: (a) for something to be a "disease", it must meet criteria which often require decades of debate and the debate is often distorted by political and economic interests; (b) the substance may only effect a "symptom" or a biomarker, which when so affected, may be a desired outcome and; (c) not all or even a majority of people can be expected to experience the same effect from a substance.

(2)(a) Agreement on a "disease". Many diseases are still unknown or undefined to the satisfaction of "mainstream science." What we may now judge to be the result of an aging process, a "bad reaction" to a food or drug, an unexplained event or worse, wrongful attribution; is all too often taking place.

- How long was "early-onset" senility diagnosed before Alzheimer's disease became known?
- How many died from unexplained cardiovascular and neurological deterioration in middle age before obstructive sleep apnea was agreed upon?
- How long was Crohn's disease or gluten-sensitivity characterized as "indigestion of unknown origin"?

That some "conditions" are identified as diseases, may have undesirable political or economic outcomes for others can easily be determined by examining some typical circumstances:

- Recognition of a disease may require coverage by health or disability insurance or pension plans;
- Certain charitable organizations and researchers have a vested interest in preserving unsolved problems and may find it difficult to make the transition to something else once the *raison d'etre* no longer exists.

(2)(b) A change in a biomarker should be sufficient basis to make a claim. The second compelling reason for the "disconnect" between substance and disease is that mitigation of a biomarker may be as important as mitigation of a disease. For example, while we know that abatement of hypertriglyceridemia or hypercholesterolemia has a statistically significant association in the reduction of risk of coronary heart disease, might there be other beneficial effects as well? Under the current system, the effect on each possible end disease would have to be tested (see also later, §(2)(c)). While the debate continues in the scientific community about the beneficial effects of decreased homocysteine levels, many educated consumers and clinical practitioners are already convinced of the need to lower these levels; further, because consumers and clinicians are convinced that the argument among scientists only has to do with efficacy and not safety, why not allow consumers a chance to produce a changed homocysteine blood level? Why not allow a truthful statement such as *"Substance X will lower homocysteine blood levels"* as a claim? Consumers will rarely agree the Agency or mainstream science moves fast enough to respond to scientific developments, so if the association between the biomarker and the substance is proven, the consumer should be allowed to make the decision for him or herself.

(2)(c) Not all consumers can be expected to benefit equally from a treatment. It has long been known that not all drugs will have the same quantitative or qualitative effects in all patients. This is logical and in practice, for example FDA CDER does not approve drugs on the basis of imputed mechanism of action, but on empirical result *e.g.,* did the drug lower blood pressure? In the past few years we have learned that efficacy is not only controlled by availability of receptor sites and metabolism, but the "-omics" of the individual (metabolomics, influencing the metabolism of the drug) and even "nutragenomics" (when certain constituents of foods (or lack of these constituents), may have a profound response on the individual *e.g.,* tyramine in fish and MOA inhibitors) and/or the ability of the individual to "up-" or "down-regulate" specific genes. Could it be that some of the several hundred "orphan diseases" are actually as yet unidentified nutritional deficiencies in those victims with the disease? The Agency cannot expect that all subjects will respond equally or even at all; the criterion for confirmation should be simply that the biomarker exhibited change in a susceptible population when treated with the substance.

(3) FDA must vest independent experts (outside of government agencies), who can make scientifically sound, unbiased decisions, with the power to judge the validity of a claim. The framers of the 1958 Amendment to the Federal Food, Drug and Cosmetic Act anticipated the logjam of food additive petitions to FDA. At that time, the Agency was understaffed, without an adequate number of scientists having the depth of experience required to make the judgment calls necessary for approval of ingredients then in use. Out of this dilemma, grew the GRAS concept, which has experienced phenomenal success. The most resounding testimony to the viability of GRAS is the fact that few GRAS determinations have been overturned and the number of GRAS substances found unsafe is vanishingly small when seen in the perspective of the large numbers of substances approved. However, the use of outside Expert (GRAS) Panels was not a first-time experiment in 1958; a similar concept, of *generally recognized as safe and effective* (GRASE), first used for animal drugs and later for over-the-counter drugs, was also successful, but has unfortunately, strayed from the path of the original intentions of the framers of the law. The spirit of outside experts was also implicit in the legislative history dealing with Significant Scientific Agreement, but the final interpretation has been that the only credible experts reside within government.

The time has come for the Agency to demonstrate its faith in the process of review by outside experts, by recognizing the opinion of outside experts as authoritative and having substance. The use of outside experts in the Qualified Health Claims proposal, only recognizes the authority of outside experts as study reviewers, with no true decision-making authority. The outside experts need to be vested with the authority to make decisions in a manner similar to the current GRAS Notification system; wherein the decision of an independent body on a particular claim may stand, following a notice of "No Objection" by the Agency. Using independent experts is the only way the faith of the consumer can be restored in an overburdened Agency whose inability to respond to consumer needs is interpreted as the ponderous nature of a bureaucracy.

(4) FDA must permit a term of exclusivity for marketing a product, if the Agency ever expects to provide the incentive for responsible manufacturers to recoup their investment in safety and efficacy testing. Under the proposed rules for Qualified Health Claims, data supporting a claim would become publicly available; also, similar claims could be "bundled" and processed as one. Public disclosure of efficacy data (not safety data) may be the single most destructive act to prevent the generation of information supporting efficacy. The lack of protection afforded to data will result in few, if any, products with sustainable claims

coming to market and will exacerbate, not cure, the problem of unsubstantiated claims by unscrupulous marketers. The consumer will become the ultimate victim of this ill-advised disclosure. Protection of efficacy data is common with drugs (with the use of a "Drug Master File") and occasionally for foods (a "Food Master File). Absence of a similar protection for ingredients for which health claims might be made will not foster the type of competition referenced in the ANPR and the type of competition needed to bring the best product possible to the public.

Disclosure of safety information, however, is logical and in the interest of public safety as safety data can be used in anticipating possible interactions with other substances (*e.g.,* drugs, food ingredients and supplements) and affording a means for analysis of adverse reactions.

In summary, FDA must re-consider some of it's basic default assumptions and assume a position of flexibility and, lastly, recognition of the folly that in the specifics of claims, there is no such thing as "one size fits all".

Sincerely,

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